

## **REMARKS AND ARGUMENTS**

### **The Status of the Claims.**

Claims 1 and 17 to 20 are pending with entry of this amendment. Claim 2 is cancelled herein, and claims 3 to 16 and 21 to 26 were previously cancelled. Claims 1 and 17 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 1 and 17, support for a double bond between the lactam and fluorescent moiety can be found throughout the specification. For example, see Figures 1, 2, 3, 4, 5 and 6, the specification in paragraph 50, and Table 1.

Applicants submit that no new matter has been added to the application by way of the above Amendment. The present amendments place the claims in condition for allowance. Accordingly, entry of the Amendments is respectfully requested.

### **35 U.S.C. §112, First Paragraph.**

Applicants very much appreciate that Examiner Berch took the time to present his perspective on the enablement of the claims essentially as presently amended. However, Applicants assert that the currently amended claims are redundantly enabled for the reasons discussed below.

In the final Office Action of November 17, 2006, claims 19 and 20 were rejected under 35 U.S.C. §112, first paragraph. To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention.

The rejections in the Action were based, e.g., on the assertion that the structures of claims "do not fall within the ambit of Formula I, to which utility is tied." Applicants note that the structures of all prior claims do fall within the bounds of general Formula I. Applicants note that the Office must interpret claim terms with reference to the

specification and to respect non-standard usage where there is express intent in a specification. "In the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art." *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003). Applicants note that such an intent to impart a novel meaning is present in the original specification. However, in the interest of cooperation and to expedite prosecution of this application, Applicants have amended claims to further clarify and unambiguously identify alternate (single or double bond linked) beta-lactamase substrates of the invention.

Although the Examiner agrees that single bonded linkers are enabled by the specification, the Advisory Action suggests, e.g., that the structure of general formula I does not include structures with a double bonded link between a lactam substrate and a fluorophore. The Advisory Action bases the argument against enablement on the contention that "figures 1-6 and paragraph 50 ... show just one Z choice, not the generic concept of any Z being double bonded to the rest of the molecule." On the contrary, as will be discussed below, the general concept of double bonding lactams to a variety of "Z" choices is expressly and redundantly stated in the original specification and reduced to practice in multiple useful examples.

#### **Compounds with Either Single and Double Bonded Linkages are Enabled.**

Support for generic Z group fluorophore linkage through either single or double bonds can be found throughout the specification. Prior Actions acknowledge that the compounds with single bonded linkages are enabled, so the following remarks will focus on double bonded embodiments.

The original specification teaches generic and specific synthesis, use and variations of beta-lactamase substrates of the invention having double bonded linkages to fluorophores. Paragraph 50 of the original specification states "[a] general method for synthesis of compounds of general formula I is depicted below (Scheme 1). As one of ordinary skill in the art will appreciate, the methods below can be used for a variety of derivatives, and other methods of synthesis are possible." Emphasis added. (Webster's "general" - **generic**; applicable to the majority.) This general synthetic scheme results in a

beta-lactam bonded to a phenolic ether fluorophore through a double bonded linker. In the next paragraph, "Table 1 depicts other cephempropenyl phenol ethers synthesized." The compounds of Table 1, were actually synthesized according to the generic method and include double bonded (cis/trans/mixed) linkers to at least two different Z groups. These compounds were found useful as substrates in the detection of beta-lactamases (see paragraph 65). In the context of the general syntheses, paragraph 52 states that "[a] large variety of phenolic fluorophores could be substituted for the resorufin ["Z"] derivative disclosed herein. Examples include the coumarin, the pyrene, and the rhodol. In each case the fluorescence is greatly enhanced [utility] and shifts to longer wavelengths when the free phenolic group is release from the ether linkage to the cephalosporin." Emphasis added. A variety of substrates with double bonds to fluorophores were described in the specification and found useful.

It is an objective fact that the original specification teaches: 1) generic and specific beta-lactamase substrates that can include either a single or double bonded linker, and 2) more than "just one Z choice" for either double or single bond linkers. Because the alternate compounds of claim 1 are taught in the specification and they are linked with common utilities, although this is not required as discussed below, there is no basis to allege lack of enablement for the claim.

With regard to the Z groups of claim 17, the actions argue that "R<sub>3</sub> is in all cases a single bond." However, R<sub>3</sub>, in amended claim 17, is not merely a bond, but is a generic linker. Again, the claim terms must be interpreted according to the express meaning found in the specification. Note that "R<sub>3</sub>" is defined in the specification as any "linker for a fluorescent donor." Note, for example, in the structure resulting in the general method of general formula I synthesis at the end of paragraph 50, the R<sub>3</sub> linker has a double bond, even though the fluorophore (one of those actually listed in claim 17) includes the single ether bond to the linker. The fact that R<sub>3</sub> can be a generic linker is further taught in Table 1 of the specification, wherein further examples of fluorophores having single bond ether groups are connected to linkers having double bonds (cis/trans/mixed) to beta-lactams. The presence of an ether bond between the fluorophore and lactam does not exclude the presence of a double

bond in the linker chemistry. Contrary to the Action, the Z groups of claim 17 do have provision for a double bond through the well defined R<sub>3</sub> group.

Clearly, the original specification enables independent claims 1 and 17, including single or double bonded linkers to a generic Z fluorophore. The argument for rejection in the previous Actions was based solely on the contention that the link to "Z" in general formula I can only be interpreted as a single bond. This point is now moot because Applicants have shown enablement of alternate formulas as currently claimed.

Rejections under 35 § 112, first paragraph enablement are often presented in terms of an alleged "undue experimentation" required to practice the invention in light of the specification. Because single bond and double bond linkage chemistries were well known in the art and because the specification teaches required linkage chemistries, no reasonable argument can be made that the linkage at issue would require undue experimentation to practice the claims. Therefore, Applicants will forego lengthy discussions of Wands factors.

#### **Utility of Claimed Embodiments.**

**I. Single and Double Bonds.** Prior Actions have suggested that double bond linked compounds of the invention are not "tied" to the utility of formula I compounds and thus allegedly fail to meet enablement standards. Applicants note that claimed compounds with independent utility are not required to be tied to the utility of other claimed compounds. Applicants assert that both single and double bonded embodiments of the inventive substrates fall within the ambit of general formula I. However, this point is moot because single and double bond linked compounds of the invention are now claimed in the alternative. Examples of independent and common utilities for the alternate compounds can be found throughout the original specification, so this line of argument for rejection is no longer supportable.

Prior Actions have acknowledged utility of substrates having single bonded linkage to fluorophores. Therefore, the following remarks will focus on support in the original specification for utility of the beta-lactamase substrates having double bonded linkage to fluorophores.

Both single bonded and double bonded embodiments, e.g., "compounds of the invention", are described in the specification as having a variety of uses. For example, the compounds are described as useful for detecting beta-lactamase activity in a host cell, monitoring expression of a gene, determining if a test compound can alter the expression of a gene, determine activation of an expression control sequence, and the like (see, e.g., figures and paragraphs 17 to 20, 68 and 69).

Generic and specific substrates having double bonded linkage to fluorophores have demonstrated utility. For example, see the as fluorogenic beta-lactamase substrates of Figures 2 and 6. The double bonded substrates of Table 1, for example are cited as actually being prepared and found to be useful in detection of beta-lactamases (see, e.g., paragraph 65).

**II. "A" Groups.** The Advisory Action suggests there may not be utility for all embodiments of the compounds wherein A is S, SO or SO<sub>2</sub>. However, any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility (MPEP 2107). Here, the specification and previous Responses provide statements, evidence and examples of utility for all claimed embodiments. The Examiner acknowledges utility of embodiments wherein A is S, but has alleged lack of utility for embodiments wherein A is SO or SO<sub>2</sub> without a statement suggesting why provided utilities allegedly would not work, or an allegation that the utilities are "insubstantial". A case for lack of utility has not been made. However, in the spirit of cooperation and to expedite the prosecution of this application, Applicants again point out the utility of these beta-lactamase substrate embodiments.

An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. The specification asserts, and Applicants hereby reassert, compounds of the invention wherein A is S or SO or SO<sub>2</sub> are useful, e.g., as beta-lactamase substrates. No Action has cited any evidence to the contrary. Furthermore, abundant specific examples are present in the specification wherein the compounds have been synthesized and shown to have characteristics useful, e.g., in beta-lactamase analyses. For example, beta-lactamase detection is shown in actual examples using the compounds wherein A is S (see, e.g., Figures

2, 8 and 9) or SO (see, e.g., Figure 6). In addition, the specification reports that all of the compounds are shown to have differing stability in Figure 4, and associated discussion. The Advisory Action suggests that no utility can be found in compounds with enhanced stability, but provides no explanation. Applicants assert that the enhanced stability of substrates can provide a variety of useful benefits such as, e.g., enhanced storage life, ability to store the substrates without refrigeration, and lowered background levels during analyses for beta-lactamases. Furthermore, the compounds of Table 1, including embodiments wherein A is S, SO or SO<sub>2</sub>, have all been identified as beta-lactamase substrates suitable for detection of beta-lactamase activity.

Again, because the claims are clearly supported by the specification with descriptions of how to make and use the claimed compounds, which plainly have utility, Applicants respectfully assert that there is no reasonable basis for continued enablement rejections.

### **Objections to the Claims**

In previous Actions, claims were objected to as allegedly not being further limiting over the independent claim 1. However, essentially as suggested by the Examiner, Applicants have amended the claims to more clearly place them in proper dependent form. That is, claim 1 has been amended, e.g., to further clarify the fact that structures of claims 19 and 20 are species of the compounds of claim 1.

### **CONCLUSION**

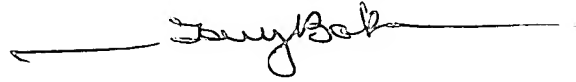
In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. Therefore, issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

Appl. No. 10/044,486  
Response Dated September 26, 2006  
Request for Continued Examination

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Respectfully submitted,

A handwritten signature in black ink, appearing to read "Gary Baker", is written over a horizontal line.

Gary Baker  
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Attachments:

- 1) A petition to extend the period of response for 4 months;
- 2) A transmittal sheet;
- 3) A fee transmittal sheet; and,
- 4) A receipt indication postcard.